AR201-14062

Karen Hoffman
11/06/2002 05:13 PM

To: Barbara Leczynski/DC/USEPA/US@EPA, NCIC HPV@EPA, Jodi Burgess/DC/USEPA/US@EPA
cc:
Subject: HPV Submission: Tetrachlorophthalic Anhydride

----- Forwarded by Karen Hoffman/DC/USEPA/US on 11/06/02 05:12 PM -----

"Johannsen, Frederick R" <frjoha@solutia.com> on 11/06/2002 03:47:08 PM

To: Rtk Chem/DC/USEPA/US@EPA
cc:
Subject: HPV Submission: Tetrachlorophthalic Anhydride

Please see attached submission....

<<HPVTETRATHALtrans.doc>> <<HPV Final TETRATHAL.doc>>
<<tcpa.rtf>>

- HPVTETRATHALtrans.doc
- HPV Final TETRATHAL.doc
- tcpa.rtf

AR201-14062A

HIGH PRODUCTION VOLUME (HPV)

CHEMICALS CHALLENGE PROGRAM

TEST PLAN

For

4,5,6,7-TETRACHLORO-1,3-ISOBENZOFURANDIONE

CAS NO. 117-08-8

Prepared by:

Solutia, Inc. Registration No.

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EXECUTIVE SUMMARY

Solutia, Inc. voluntarily submits the following screening information data and test plan covering the chemical, 4,5,6,7-Tetrachloro-1,3-isobenzofurandione, also known as Tetrachlorophthalic Anhydride or TCPA (CAS No. 117-08-8), for review under the Environmental Protection Agency's High Production Volume (HPV) Chemicals Challenge Program.

A substantial amount of data exists to evaluate the potential hazards associated with TCPA. Use of key studies or estimation models available from data already developed provide adequate support to characterize the Endpoints in the HPV Chemicals Challenge Program without the need for additional, unnecessary testing.

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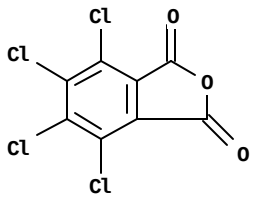
TEST PLAN FOR TETRACHLOROPHTHALIC ANHYDRIDE

I. INTRODUCTION AND IDENTIFICATION OF CHEMICAL

Under EPA's High Production Volume (HPV) Chemicals Challenge Program, Solutia Inc. has committed to voluntarily compile basic screening data on Tetrachlorophthalic Anhydride, also known as TCPA. The data included in this Test Plan provide physicochemical properties, environmental fate, and human and environmental effects of TCPA, as defined by the Organization for Economic Cooperation and Development (OECD). The information provided comes from existing data developed on behalf of Solutia Inc. or found in the published scientific literature and fulfills Solutia's obligation to the HPV Challenge Program.

A. Structure and Nomenclature

Following is a structural characterization of TCPA and associated nomenclature.



Phthalic anhydride, tetrachloro-
CAS No. 117-08-8

Synonyms: 4,5,6,7-Tetrachloro-1,3-isobenzofurandione; TCPA; TETRATHAL ®, Tetrachlorophthalic Anhydride; CP 626.

B. Manufacturing & Use

TCPA is manufactured by a single US producer, Solutia Inc., at a single manufacturing site and is produced in short production campaigns. The manufacturing operation is a closed, continuous process. Due to its potential to cause occupational asthma (Schlueter et al, 1978), Solutia has adopted an airborne exposure guideline of 0.5 mg/m^3 8-hour TWA and a 1 mg/m^3 15-minute TWA for this compound. Employees wear eye and skin protection to prevent contact and approved respiratory protection equipment, should

airborne exposure limits be exceeded. Only a few employees are involved in the manufacturing process and thus have minimal potential for skin or airborne exposure, and those chiefly during drying and material transfer operations.

TCPA is sold to a limited number of customers at a few processing sites. Over 70% of annual production is exported from the US (NTP, 1993). TCPA is used primarily as (1) a chemical intermediate which undergoes chemical reaction to form chemicals used as dyes/pigments and as (2) a "reactive type" flame retardant in plastics (epoxy resins, polyesters, and polyurethanes). This designation is indicative that TCPA reacts to become chemically bound to the polymer backbone of the plastic (NTP, 1993). There are no known consumer uses of TCPA. Thus, potential exposure to TCPA resulting from TSCA-related activities is negligible. Airborne losses during manufacturing and during use have been estimated to be 0.05 pounds per 1000 pounds consumed (NTP, 1993). Hence, very limited occupational or environmental exposure is expected to occur.

II. TEST PLAN RATIONALE

The information obtained and included to support this Test Plan have come from either 1) internal studies conducted by/or for Solutia Inc. (or its predecessor Monsanto Co.), 2) have been extracted from the scientific literature either as primary references or as found in well-accepted, peer-reviewed reference books, or 3) were estimated using environmental models accepted by the US EPA (1999b) for such purposes. This initial assessment includes information on physicochemical properties, environmental fate, and human and environmental effects associated with TCPA. The data used to support this program include those Endpoints identified by the US EPA (1998); key studies have been identified for each data Endpoint and summarized in Robust Summary form and included in Section VI. of this Dossier.

All studies were reviewed and assessed for reliability according to standards specified by Klimisch *et al* (1997), as recommended by the US EPA (1999a). The following criteria were used for codification:

1. Reliable without Restriction - Includes studies which comply with US EPA and/or OECD-accepted testing guidelines, which were conducted using Good Laboratory Practices (GLPs) and for which test parameters are complete and well documented,

2. Reliable with Restrictions – Includes studies which were conducted according to national/international testing guidance and are well documented. May include studies conducted prior to establishment of testing standards or GLPs but meet the test parameters and data documentation of subsequent guidance; also includes studies with test

parameters which are well documented and scientifically valid but vary slightly from current testing guidance. Also included were physical-chemical property data obtained from reference handbooks as well as environmental endpoint values obtained from an accepted method of estimation (i.e. EPIWIN).

3.Not Reliable – Includes studies in which there are interferences in either the study design or results that provide scientific uncertainty or where documentation is insufficient.

4. Not Assignable – Used to identify Supplemental studies conducted according to methodology insufficient to fully support an Endpoint in the HPV assessment program.

Those studies receiving a Klimisch rating of 1 or 2 are considered adequate to support data assessment needs in this Dossier. A few additional studies with TCPA have been identified during our literature search on the referenced HPV Endpoints but have not been summarized in this Dossier. The data herein presented is considered typical of additional information located in our literature review.

III. TEST PLAN SUMMARY AND CONCLUSIONS

Conclusion: Nearly all HPV Endpoints have been satisfied with data from studies that were either well documented, used OECD guideline methods and conducted in accord with GLPs, or were estimated from acceptable estimation modeling programs. In those cases where data were not available, use of the weight-of-evidence has been applied to support a conclusion that no additional information is needed. Hence, no further testing for any of the HPV Endpoints is deemed necessary, as summarized in Table 1.

In summary:
Physical-chemical property values (Melting Point, Boiling Point, Vapor Pressure, Partition Coefficient and Water Solubility) were obtained from reputable reference books and further cited as an Accepted or Peer Reviewed value in the Hazardous Substances Data Bank - Tetrachlorophthalic Anhydride (2002) and/or summarized in the NTP Toxicity Report No. 28 – Tetrachlorophthalic Anhydride (1993). Thus, these values were classified as "2-Reliable with restrictions".

Environmental Fate values for Photodegradation, and Transport (Fugacity) were obtained using a computer estimation –modeling program (EPIWIN, 2002) recommended by EPA; as such, they were designated "2-Reliable with restrictions". The EPIWIN program was unable to estimate Stability in Water (Hydrolysis). Due to its limited environmental exposure potential and the stated recognition of hydrolysis from the anhydride to its acid form (US EPA, 1982), no additional Hydrolysis testing is deemed needed to fill this Endpoint. Due to its insolubility, Biodegradation testing

(SCAS test) of TCPA could not be conducted even after several trials. Therefore, a biodegradaton study was conducted with the sodium salt of tetrachlorophthalic acid. That study was well-documented and was conducted using methodology that preceded, but is considered consistent with, methodology recommended in OECD test guideline 301.

Ecotoxicity - A study conducted according to OECD guidelines for Acute Invertebrate Toxicity (OECD 202) and designated "2- Reliable with restrictions" fulfilled this Endpoint requirement. No acceptable studies were found to address either the Acute Plant Toxicity or the Acute Fish Toxicity Endpoint. Based on estimated levels of toxicity in fish and invertebrates occurring only above the level of TCPA water solubility, no additional testing is warranted for these two Endpoints.

Mammalian Toxicity Endpoints (Acute Toxicity, Repeated Dose Toxicity, Ames and Chromosomal Aberration Testing, and Reproductive Toxicity) have all been filled with tests that either conformed directly with OECD test guidance or followed test designs similar to OECD guidance.

The Acute Toxicity Endpoint was supported by an oral toxicity study which was conducted preceding codification of OECD and GLP guidance but was well documented and followed methodology consistent with later guidance; it is considered "2- Reliable with restrictions".

The Repeated Dose Toxicity Endpoint was met with a 90-Day Subchronic rat study (similar to OECD guideline 408) conducted in accordance with GLPs. It also was codified as "2- Reliable with restrictions" due to minor deviations in methodology.

Both the Ames test and the *in vitro* Chromosomal Aberration assay used to support their respective Endpoints were conducted by the US National Toxicology Program (NTP). The Ames test followed a study design equivalent to OECD guideline # 471 while the cytogenetics study was similar to, but not identical with, OECD guideline # 473. Thus, the Ames test was categorized as "1- Reliable without restriction" while the Cytogenetics study was classified as "2- Reliable with restrictions".

The Reproductive Toxicity HPV Endpoint has been filled using a combination of the 90-day Subchronic Rat study previously cited along with a Rat Developmental Toxicity study, the latter considered "1- Reliable without restriction". Both studies met respective OECD test guidelines, i.e. OECD 408 and 414 and were conducted according to GLP guidance. No effects on male or female reproductive organs were observed in the Subchronic study. Therefore, according to EPA Guidance (US EPA, 1998), use of this combination of tests can fulfill this HPV Reproductive Toxicity Endpoint.

Following is a tabular summary of the Test Plan developed for Tetrachlorophthalic Anhydride.

Table 1. Test Plan Matrix for Tetrachlorophthalic Anhydride

	Info. Avail.	OECD	GLP	Other Study	Estimat. Method	Accept-Able ?	Testing Recomm.
PHYSICAL CHEMICAL							
Melting Point	Y	R	N	N	-	Y	N
Boiling Point	Y	R	N	N	-	Y	N
Vapor Pressure	Y	R	N	N	-	Y	N
Partition Coefficient	Y	R	N	N	-	Y	N
Water Solubility	Y	R	N	N	-	Y	N
ENVIRONMENTAL FATE ENDPOINTS							
Photodegradation	Y	N	N	N	Y	Y	N
Stability in Water	N	-	-	N	-	-	N
Biodegradation	Y	N	N	Y	-	Y	N
Transport between Environmental Compartments (Fugacity)	Y	N	N	N	Y	Y	N
ECOTOXICITY							
Acute Toxicity to Fish	Y	N	N	Y	Y	Y	N
Acute Toxicity to Aquatic Invertebrates	Y	Y	Y	N	-	Y	N
Toxicity to Aquatic Plants	Y	-	-	-	Y	Y	N
MAMMALIAN TOXICITY							
Acute Toxicity	Y	N	N	Y	-	Y	N
Repeated Dose Toxicity	Y	Y	Y	Y	-	Y	N
Genetic Toxicity – Mutation (Ames)	Y	Y	Y	Y	-	Y	N
Genetic Toxicity – Chromosomal Aberrations	Y	N	Y	Y	-	Y	N
Developmental Toxicity	Y	Y	Y	N	-	Y	N
Reproductive Toxicity	Y	-	-	Y	-	C	N

Y = Yes; N = No; R = Reference value; C = Completed through combination of Developmental Toxicity and Subchronic Toxicity Endpoints; - = Not applicable

III. DATA SET SUMMARY AND EVALUATION

The key studies used in this assessment to fulfill the HPV requirements have been placed in an Endpoint-specific matrix, and further discussed below. Robust Summaries for each study referenced can be found in Section VI of this Dossier.

A. Chemical/Physical Properties

Table 2. Selected Chemical/Physical Properties of Tetrachlorophthalic Anhydride (TCPA)

Chemical	Boiling Pt. (^{o}C.)	Melting Pt.(^{o} C.)	Vapor Pressure (hPa @ 145 ^{o}C)	Water Solubility (mg/L)	Partition Coefficient (Log Kow)
TCPA CAS No. 117-08-8	371	254.5	0.21	< 1.0 @ 21 ^{o}C.	3.57

All HPV Endpoints for Physical-Chemical Properties have been completed with reliable information and taken from reputable textbook-references (Table 2). The values, which have been designated as "2-Reliable with restrictions", are included in the Robust Summary section of this Dossier, have been accepted as accurately depicting the properties of TCPA and are cited as peer-reviewed references in the Hazardous Substances Data Bank for Tetrachlorophthalic Anhydride (HSDB, 2002) and/or the NTP Technical Report on Toxicity of Tetrachlorophthalic Anhydride (1993).

In summary, these data indicate that TCPA is a solid at room temperature and has a low vapor pressure. It has a moderate octanol:water partition coefficient and very low solubility in water.

Conclusion – Adequate reference values are available to provide needed information on the Physical-Chemical Properties associated with TCPA. Therefore, no additional data development is needed for these HPV Endpoints.

B. Environmental Fate and Biodegradation

In-house attempts to conduct a Semi-Continuous Activated Sludge (SCAS) Biodegradability study with TCPA proved unsuccessful, due to its very low water solubility. Therefore, a SCAS test was conducted with the sodium salt of TCPAcid. That study is summarized in the Robust Summary section of this Dossier and cited in Table 3

below. While conducted prior to inception of standardized international guidelines for **Biodegradability** testing and GLPs, this study followed similar standards for conduct subsequently codified into OECD guideline 301 and GLP documentation. Due to the technical difficulties to be encountered to conduct such a study with TCPA, no future attempts at testing are planned.

No information could be located regarding Photodegradation, Stability in Water (Hydrolysis) and Transport (Fugacity) for TCPA following an extensive literature search. Thus, we have incorporated the use of the estimation models found in EPIWIN (2002) for determination of these HPV Endpoints and have been designated "2-Reliable with restrictions". Estimated **Photodegradation** Rate and **Fugacity** values are cited with the Robust Summaries and also are included in Table 3; thus, these HPV Endpoints are considered complete and each judged as "2-Reliable with restrictions". In deference to this estimated Photodegradation rate, we note the information reported by Yu and Atallah (1978) with a structurally similar chemical, Tetra**bromo**phthalic anhydride (TBPA)(CAS No. 632-79-1). When TBPA was applied to silica gel surfaces and irradiated with UV light, it was demonstrated to hydrolyze rapidly (half life of less than 5 min.) to the dicarboxylic acid; this result is also consistent with its degradation pattern in moist soil (Butz and Atallah, 1979). A similar, rapid hydrolysis after UV exposure, would be expected to occur with TCPA.

No data is available on Stability of TCPA in Water and the EPIWIN (2002) program is not capable of estimating a hydrolysis value for cyclic esters, including TCPA. Thus, the water stability of TCPA is best estimated from analogy with related compounds, as it is impossible to conduct the recommended OECD 111 test with this material. The OECD 111 test requires the test material to be soluble at a level of 20 mM, and the actual water solubility of TCPA is < 1 mg/L, or < 0.004 mM, thus rendering this study impractical to conduct.

TCPA is an anhydride, a reactive species known to be readily hydrolysable (Smith and March, 2001). The presence of the electron-withdrawing chloro groups are also expected to increase the susceptibility to base hydrolysis by reducing electron density at the carbonyl carbon and making the meta carboxyl group a better leaving group. Thus, the tetrachloro compound should hydrolyze even more rapidly than phthalic anhydride, which is reported to have a $T_{1/2}$ in water of about 90 seconds (Jones, HR, 1972). TCPA is already expected to hydrolyze to its acid (US EPA, 1982). While the acid itself is only slightly soluble and has shown little biodegradation potential in the SCAS test (Table 3), it is considered biodegradable in the environment under both aerobic and anaerobic conditions (Bosma et al, 1996).

By way of comparison, the structurally similar TBPA (Tetrabromophthalic anhydride) has been assessed for its capacity to hydrolyze in moist soils (Butz and Atallah, 1979). Rapid hydrolysis occurred to the halogenated phthalic acid, where further degradation ceased.

Table 3. Environmental Fate and Biodegradation Parameters for Tetrachlorophthalic Anhydride (TCPA)

Chemical	Biodegradation Rate	Stability in Water	Fugacity (%)	Photodegrad. Rate (T ½)
TCPA CAS No. 117-08-8	0.2 %	Not calculatable In EPIWIN, but Considered rapid	Air – 1.25 Water – 13.4 Soil – 83.9 Sediment – 1.42	338.4 days-EPIWIN. Hydrolysis - rapid

The Environmental Fate and Biodegradability of TCPA can be summarized as follows. Upon release to the air, TCPA is expected to react photochemically only to a minimal extent by reaction with photochemically-produced hydroxyl radicals; the half-life for this reaction in air is estimated to be 338 days (Table 3 - Photodegradation). It is anticipated that rapid hydrolysis would occur. The majority of airborne TCPA or its acid equivalent would be expected to precipitate in the soil (Table 3 – Fugacity). If still in its parent form it would undergo rapid hydrolysis in a moist soil environment, and much would become soil-bound. Significant volatilization from soil or water to air is not expected, based on its Vapor Pressure (Table 2) and Henry's Law constant (EPIWIN, 2002). In aqueous solution, TCPA is expected to hydrolyze to its acid form and thereafter undergo further aerobic and anaerobic degradation (Bosma et al, 1996). Due to TCPA's low water solubility and high binding capacity, the potential for persistence or bioaccumulation has been judged as minimal (US EPA, 1982).

Conclusion – Adequate studies are available to provide needed information for the HPV Designated Environmental Properties associated with TCPA. Biodegradation with its sodium salt used methodology consistent with OECD test guidance, while Fugacity and Photodegradation Endpoints were completed using EPIWIN, an accepted estimation-modeling program. Justification for no additional testing needs for Stability in Water is based on known hydrolysis of anhydrides and low solubility that prevents conduct of a meaningful study. Therefore, it is concluded that no additional data development is needed for these HPV Endpoints.

C. Aquatic Toxicity

Limited information is available on the acute toxicity of TCPA on algae, invertebrates and fish. An acceptable study, summarizing effects in *D. magna* has been used to fulfill the Acute Invertebrate Toxicity Endpoint. While not conducted specifically to meet OECD guidelines, it used methodology recommended by the US EPA Committee of Methods for Toxicity Testing with Aquatic Organisms (1975). These recommendations are consistent with OECD guidelines; the study was conducted under GLPs. The study

was conducted at and above levels of TCPA water solubility (<1 ppm); while this does not detract from the lack of toxicity seen up to that level, the final nominal LC0 (Minimum Lethal Dose) value reported of > 1,000 ppm is well above TCPA solubility and thus artificially elevated. Hence, this study has been designated as "2- Reliable with restrictions", selected for development of Robust Summaries, and is cited in Table 4. A computer-derived estimation of a 48-hr. Daphnia LC50 value with TCPA correctly indicated a toxicity value in excess of the water solubility of TCPA, as was determined in the present study.

Table 4. Aquatic toxicity parameters for Tetrachlorophthalic Anhydride (TCPA)

Chemical	Fish LC 50 (mg/L)	Invertebrate LC50 (mg/L)	Algae EC50 (mg/L)
TCPA CAS No. 117-08-8	7.086 (estim.)	> 1,000 (Daphnia-48 hr)	5.791 (estim.)

No adequate toxicity study data has been located to fulfill the Acute Fish Toxicity and the Acute Algae Toxicity Endpoints. A single preliminary acute fish toxicity study (Applegate et al, 1957) reported the lack of toxicity to sea lamprey larvae after static exposure to a nominal concentration of 5 ppm TCPA; this again was conducted at a level well above TCPA water solubility. This study is considered insufficient in design and documentation (Category 3) to justify use in completion of this HPV data set and has not been summarized further. However, no effects of exposure were observed at the test level reported.

We have conducted a computer-derived (ECOSAR) toxicity value to aquatic species for TCPA. Levels of predicted toxicity for both fish and algae are cited in Table 4 and have been further summarized in section VI. Robust Summaries of this Dossier; TCPA-specific parameters used in the modeling are cited.

Additionally, acute static toxicity studies in fish (rainbow trout and bluegill sunfish) and water fleas (D. magna) have been reported for the structurally similar chemical tetrabromophthalic anhydride (TCBA) (US EPA 1986a, 1986b, 1986c). In all cases, the LC50 values were reported to be greater than 10 mg/L TBPA.

Based on the weight-of-information available on TCPA, we conclude that no additional testing for either of the Fish or Algae Toxicity Endpoints appears justified. We base this conclusion on the following lines of evidence: (1) TCPA is nearly insoluble (solubility level of <1ppm) in water, (2) TCPA is not toxic (LC0) at aqueous levels of saturation, (3) predictive modeling estimates that aquatic toxicity of TCPA could only occur above the level of TCPA water solubility, hence that limit already sets the upper bound of potential toxicity (4) TCPA's expected pattern and release scenarios and its projected environmental pathways indicate a negligible presence in the aquatic domain and (5) results of a close structural analog (TBPA) proved non toxic to fish and invertebrates.

Conclusion – An adequate study is available to meet the Acute Invertebrate Toxicity Endpoint for TCPA. Further, results of the lack of toxicity, coupled with low water solubility and insignificant environmental levels in the aquatic environment mitigates against any additional, unnecessary testing to complete additional HPV Endpoints in this category.

D. Mammalian Toxicity Endpoints

A summary of available toxicity data used to fulfill the HPV Endpoints for Mammalian Toxicity is found in Tables 5 and 6. Each report citation has been further summarized in the Robust Summary section of this Dossier.

Table 5. Acute and Repeated Dose Mammalian Toxicity of Tetrachlorophthalic Anhydride (TCPA)

Chemical Name/ CAS no.	Acute Toxicity (LD50/LC50)			Subchronic (13-week) Toxicity	
	Oral (mg/kg)	Dermal (mg/kg)	Inhalation (mg/m3)	Oral (gavage)	Inhalation
Tetrachlorophthalic Anhydride CAS No. 117-08-8	>15,800	>5,010	>3,600	Rat – NOEL < 94 mg/kg Target tissue: kidneys Mice – NOEL 187 mg/kg Target tissue: none	Rat (dust) – NOEL < 0.73 mg/m3 Target tissue: lungs, liver Rat (fumes) – NOEL < 0.5 mg/m3 Target tissue: lungs., liver

1.0 Acute Toxicity

Results of acute toxicity studies by the oral, dermal and inhalation routes of exposure have been conducted, as summarized in Table 5. The oral toxicity study has been selected to fulfill the HPV Acute Toxicity Endpoint, while the other studies are included as supplemental information. Both the oral and dermal studies were conducted using study designs consistent with OECD Test Guidelines 401 and 402, respectively, and GLP guidance, but were completed before such guidance was codified. They are considered well documented and thus have been classified as "2- Reliable with restrictions". The inhalation study has been similarly classified, although its documentation is limited.

TCPA is considered to be "practically nontoxic" after acute oral or dermal exposure to rats or rabbits, respectively, and only "slightly toxic" after acute inhalation exposure. However, based on the ability of TCPA to produce allergic skin and respiratory sensitization, this material is considered to be hazardous in the workplace, requiring adequate handling practices to avoid acute or repeated exposures.

Conclusion – A quality study is available to assess the Acute hazards associated with TCPA. Therefore, no additional data development is needed for the Acute Toxicity HPV Endpoint.

2.0 Repeated Dose Toxicity

TCPA has been adequately tested by several routes of exposure to define its Repeated Dose toxicity. The key study used for this HPV assessment is cited in Table 5 and summarizes a 90-day subchronic rat study by the oral route. This study was conducted using a study design consistent with OECD Test Guideline 408, and conducted under GLP auspices as part of the NTP Testing program; it is considered "2- Reliable with restrictions" having but minor deviations from Guideline # 408. Another 90-day subchronic oral study, this one conducted in mice, was also included in the NTP testing program and also has been referenced in Table 5. While not used to support the Repeated Dose HPV Endpoint, it too is considered "2- Reliable with restrictions". Two subchronic studies conducted on behalf of Solutia Inc. with forms of TCPA dust have also been summarized in Table 5 and included in the Robust Summary section of this Dossier as Supplemental information. Each of these inhalation studies have been classified as "2- Reliable with restrictions" in that technical difficulties precluded a definitive dosage delivery determination at the lowest dosage level tested. Nevertheless, the toxicological effects reported in these studies are relevant. In all cases, no evidence of an effect on the male or female reproductive organs (including testes) was observed. Lungs and liver proved to be target tissues in the rat inhalation studies, while oral studies identified degenerative renal changes in rats, but not mice.

Conclusion - The Repeated Dose HPV Endpoint for TCPA has been fulfilled with a well-conducted and documented 90-Day Subchronic study in rats deemed "2- Reliable with restrictions". No further testing is needed for completion of information related to the Repeat Dose HPV Endpoint.

3.0 Mutagenicity and Chromosomal Aberrations

Table 6. Mutagenic and Reproductive/Developmental Mammalian Toxicity of Tetrachlorophthalic Anhydride (TCPA)

Chemical Name/ CAS no.	Mutagenicity			Reprotoxicity	Developmental. Tox
	Ames	Chromos. Aberration In vitro	Other In vitro	Other	Rat - oral
Tetrachloro phthalic Anhydride CAS No. 117-08-8	Neg w/wo S9.	Neg. w/wo S9	Neg. SCE – .w/wo S9	Mouse Sperm morph & vaginal cytol. – Both negative	Maternal & Developmental NOEL – 1000 mg/kg

3.1 Ames/Point Mutation Testing

When tested in the standard Ames assay for point mutations, TCPA elicited no mutagenic response in any of the *S. Typhimurium* tester strains employed, either with or without inclusion of metabolic activation. The Zeiger et al, (1985) study, conducted on behalf of the NCI/NTP program, has been summarized in the Robust Summary section of this Dossier and referenced in Table 5. Its design and documentation are such that it is considered equivalent to OECD guideline # 471 and thus is considered "1- Reliable without restriction" for this assessment. Additionally, TCPA has been tested in the secondary tier *Drosophila* Sex-Linked Recessive Lethal assay; no mutagenicity was observed after either oral or injection dosing up to lethal doses by each route in this same NCI/NTP program (Valencia et al, 1985).

Thus, it is concluded that adequate testing of sufficient quality to be designated "1- Reliable without restriction" has been performed on TCPA to evaluate the Ames Test (Point Mutation) requirement; no further testing is needed for this Endpoint.

3.2 - Chromosomal Aberrations

As part of the NCI/NTP program (Galloway et al, 1987), TCPA was tested in the CHO cell *in vitro* assay to determine its potential to induce chromosomal aberrations. A Robust Summary has been prepared for this study as found in section VI of this Dossier and is referenced in Table 5. As part of the same study design, the effect of TCPA treatment on production of Sister Chromatid Exchanges (SCE's) was also evaluated in the same test

system (Galloway et al, 1987). In both cases, with and without metabolic activation, TCPA was without effect. The quality of this study is considered to be "2- Reliable with restrictions", as it did not follow an established OECD protocol, yet was well documented and has been used for regulatory purposes.

TCPA has also been tested *in vivo* for induction of SCEs and Chromosomal Aberrations in mouse bone marrow cells. However, NTP has considered this study "incomplete" (NTP, 1993) and thus has not been further summarized.

The HPV Chromosomal Aberration Endpoint for testing of TCPA has, thus, been fulfilled with an adequately conducted and documented *in vitro* study; thus, no further testing is needed.

4.0 Reproductive and Developmental Toxicity

Sperm morphology and vaginal cytology evaluations were included as part of the 13-week rodent study program conducted by NTP with both mice and rats (NTP, 1993). Both studies were considered well documented but insufficient to provide definitive information to be used in this HPV assessment for TCPA and thus were designated as "4-Not assignable". Each study has been summarized in the Robust Summary section of this Dossier as Supplemental information and referenced in Table 6.

Of interest, it was concluded that there were no treatment-related changes in sperm morphology or vaginal cytology between TCPA-treated rats or mice and their respective controls (NTP, 1993).

Of direct relevance to completion of the Reproductive Toxicity Endpoint for this HPV assessment with TCPA, is identification of a well documented rat developmental toxicity study conducted according to OECD Guideline 414. This study has been assessed as "1- Reliable without restriction". It has been summarized in the Robust Summary section of this Dossier and is included in Table 6.

No maternal toxicity, embryotoxicity, fetotoxicity or teratogenic effects were observed at or below 1,000 mg/kg/d (NOEL). A low incidence of rib and vertebral malformations was observed at the maternally toxic level of 2,000 mg/kg/d. Hence, a wide margin (>10,000-fold) of safety exists at the recommended occupational exposure limit.

In conclusion, the Reproductive Toxicity HPV Endpoint has been fulfilled using the EPA-accepted (US EPA, 1998) approach of dual consideration of a 90-day subchronic study (without testicular effects) and a rodent developmental toxicity study. The available data set on TCPA conforms to this approach. Multiple repeated dose studies have been conducted, none of which are indicative of an effect on reproductive organs, including the testes, of rodents. The Repeated

Dose Study selected is of 90 days duration and of adequate quality. Similarly, a Developmental Toxicity study, assessed as "1- Reliable without restriction", has been conducted with TCPA. Thus, the data requirements for this HPV Endpoint have been met and no further testing is required.

IV. REFERENCES

Applegate, VD, Howell, JH, Hall, Jr., AB, and Smith, MA. 1957. Toxicity of 4,346 chemicals to larval lampreys and fishes. US Dept. of the Interior. Special Scientific Report – Fisheries No. 207. Washington, DC.

Bosma, TNP, Ballemas, EMW, Hoekstra, NK, Tewelscher, RAG, Smeenk, JGMM, Schraa, G and Zehnder, AJB. 1996. Biotransformation of organics in soil columns and an infiltration area. Ground Water 34:49-56.

Butz, RG and Atallah, YH. 1979. Effects of PHT-4 on soil microflora at level of 10 mg/g. Velsicol Chemical Corp. Chicago, Il. NTIS OTS0523290.

EPIWIN. 2002. Version 3.10, Syracuse Research Corporation, Syracuse, New York.

Galloway, SM, Armstrong, MJ, Reuben, C, Colman, S, Brown, B, Cannon,C, Bloom, AD, Nakamura, F, Ahmed, M, Duk, S, Rimpo, J., Margolin, BH, Resnick, MA, Anderson,B and Zeiger, E. 1987. Chromosome aberrations and sister chromatid exchanges in Chinese Hamster Ovary Cells: Evaluation of 108 chemicals. Environ Mol Mutagen 10:1-175.

Hazardous Substances Data Bank (HSDB) for Tetrachlorophthalic Anhydride, 2002.

Jones, HR. 1972. *Environmental Control in the Organic and Petroleum Industries*, Noyes Data Corp. New York, NY, USA, as cited in *Dictionary of Substances and their Effects, 2nd Electronic Edition*.

Klimisch, H.-J., Andreae, M. and Tillman, U. 1997. A systemic approach for evaluating the quality of experimental toxicological and ecotoxicological data. Regul. Toxicol. Pharmacol. 25:1-5.

National Toxicology Program (NTP). 1993. Technical Report on toxicity of Tetrachlorophthalic anhydride administered by gavage to F344/N rats and B6C3F1 mice. Toxicity Report Series No. 28, NTIS PB94119245.

Schlueter, DP, Banaszak, EF, Fink, JN, and Barboriak, J. 1978. Occupational asthma due to tetrachlorophthalic anhydride. J. Occup. Med. 20:183-186.

Smith, MS and March, J. 2001. March's Advanced Organic Chemistry, 5th Ed. Wiley Interscience, pp 469.

US EPA. 1975. Committee of Methods for Toxicity Testing with Aquatic Organisms. Methods of acute toxicity tests with fish, macroinverterates and amphibians. US EPA Ecol. Res. Ser. 660/3-75009.

US EPA, 1982. Preliminary Information Review-Tetrachlorophthalic Anhydride. PIR-317. EPA Contract No. 68-01-5789 as cited in NTIS PB94119245.

US EPA, 1986a. TSCA Submission. 86-900000289.

US EPA, 1986b. TSCA Submission 86-900000290.
US EPA, 1986c. TSCA Submission 86-900000291.

US EPA, 1998. Guidance for meeting the SIDS requirements (The SIDS Guide). Guidance for the HPV Challenge Program (11/31/98).

US EPA, 1999a. Determining the adequacy of existing data. Guidance for the HPV Challenge Program (2/10/99).

US EPA, 1999b. The use of structure-activity relationships (SAR) in the High Production Volume Chemicals Challenge Program. OPPT, EPA.

Valencia, R, Mason, JM, Woodruff, RC and Zimmering, S. 1985. Chemical mutagenesis testing in Drosophila. III. Results of 48 coded compounds tested for the National Toxicology Program. Environ Mutagen 7:325-348.

Yu, CC and YH Atallah. 1978. Photolysis of PHT-4. Velsicol Chemical Corp. Ann Arbor, MI. NTIS OTS0523289.

Zeiger, E, Haworth, S, Mortelmans, K and Speck, W. 1985. Mutagenicity testing of di(2-ethylhexyl)phthalate and related chemicals in Salmonella. Environ Mutagen 7:213-232.

V. ROBUST STUDY SUMMARIES -

IUCLID Data Sets are Appended

AR201-14062B

IUCLID

Data Set

Existing Chemical	:	ID: 117-08-8
CAS No.	:	117-08-8
EINECS Name	:	Tetrachlorophthalic Anhydride
TSCA Name	:	1,3-Isobenzofurandione, 4,5,6,7-tetrachloro-

Producer Related Part

Company	:	Solutia Inc.
Creation date	:	06.06.0002

Substance Related Part

Company	:	Solutia Inc.
Creation date	:	06.06.0002
Memo	:	
Printing date	:	02.11.2002
Revision date	:	
Date of last Update	:	02.11.2002
Number of Pages	:	25
Chapter (profile)	:	Chapter: 1, 2, 3, 4, 5, 7
Reliability (profile)	:	Reliability: without reliability, 1, 2, 3, 4
Flags (profile)	:	Flags: without flag, confidential, non confidential, WGK (DE), TA-Luft (DE), Material Safety Dataset, Risk Assessment, Directive 67/548/EEC, SIDS

1.0.1 OECD AND COMPANY INFORMATION

06.06.2002

1.0.2 LOCATION OF PRODUCTION SITE

1.0.3 IDENTITY OF RECIPIENTS

1.1 GENERAL SUBSTANCE INFORMATION

1.1.0 DETAILS ON TEM PLATE

1.1.1 SPECTRA

1.2 SYNONYMS

1.3 IMPURITIES

1.4 ADDITIVES

1.5 QUANTITY

1.6.1 LABELLING

1.6.2 CLASSIFICATION

1.7 USE PATTERN

1.7.1 TECHNOLOGY PRODUCTION/USE

1.8 OCCUPATIONAL EXPOSURE LIMIT VALUES

1.9 SOURCE OF EXPOSURE

1.10.1 RECOMMENDATIONS/PRECAUTIONARY MEASURES

1.10.2 EMERGENCY MEASURES

1.11 PACKAGING

1.12 POSSIB. OF RENDERING SUBST. HARMLESS

1.13 STATEMENTS CONCERNING WASTE

1.14.1 WATER POLLUTION

1.14.2 MAJOR ACCIDENT HAZARDS

1.14.3 AIR POLLUTION

1.15 ADDITIONAL REMARKS

1.16 LAST LITERATURE SEARCH

1.17 REVIEWS

1.18 LISTINGS E.G. CHEMICAL INVENTORIES

2.1 MELTING POINT

Value	:	= 254.5 ° C
Sublimation	:	
Method	:	other
Year	:	1979
GLP	:	no
Test substance	:	no data
Reliability	:	(2) valid with restrictions Acceptable reference text.
Flag	:	Critical study for SIDS endpoint

24.10.2002 (13)

2.2 BOILING POINT

Value	:	= 371 ° C at
Decomposition	:	
Method	:	other
Year	:	1977
GLP	:	no
Test substance	:	no data
Reliability	:	(2) valid with restrictions Acceptable reference text. Consistant with EPIWIN calculated value of 346 degrees C.
Flag	:	Critical study for SIDS endpoint

24.10.2002 (3)

2.3 DENSITY

2.3.1 GRANULOMETRY

2.4 VAPOUR PRESSURE

Value	:	.21 hPa at 145° C
Decomposition	:	
Method		other (measured)
Year	:	
GLP	:	no
Test substance	:	no data
Conclusion		EPIWIN calculated value of 5.16E-007 mm/Hg using modified Grain method; model is accepted tool for this purpose.
Reliability	:	(2) valid with restrictions Acceptable reference text.
Flag	:	Critical study for SIDS endpoint

24.10.2002 (3)

2.5 PARTITION COEFFICIENT

Log pow	:	= 3.57 at ° C
Method		other (calculated)
Year	:	1978

GLP	:	no
Test substance	:	no data
Method	:	Log P value
Conclusion	:	Consistent with Log KOW value of 4.65. using KOWWIN in EPIWIN, an accepted estimation model
Reliability	:	(2) valid with restrictions Reliable reference value from Leo, AJ. 1978. Report on the Calcuation of octanol/water Log P values for structures in EPA files.
Flag	:	Critical study for SIDS endpoint

24.10.2002

2.6.1 WATER SOLUBILITY

Value	:	< 1 mg/l at 21 ° C
Qualitative	:	
Pka	:	at 25 ° C
PH	:	at and ° C
Method	:	other
Year	:	
GLP	:	no
Test substance	:	no data
Reliability	:	(2) valid with restrictions Reference value consistent with WSKOW calculated value of 1.59 mg/L. using EPIWIN, an accepted derivation model.
Flag	:	Critical study for SIDS endpoint

24.10.2002 (4)

2.6.2 SURFACE TENSION

2.7 FLASH POINT

2.8 AUTO FLAMMABILITY

2.9 FLAMMABILITY

2.10 EXPLOSIVE PROPERTIES

2.11 OXIDIZING PROPERTIES

2.12 ADDITIONAL REMARKS

3.1.1 PHOTODEGRADATION

Indirect photolysis

Sensitizer	:	
Conc. of sens.	:	
Rate constant	:	= .0000000000000316 cm3/(molecule*sec)
Degradation	:	= 50 % after 338.4 day
Deg. Product	:	
Method	:	other (calculated)
Year	:	2002
GLP	:	no
Test substance	:	
Method	:	Used AOP Computer program, ver 1.90, Syracuse Research Corp. The AOP program estimates the rate constant for the atmospheric, gas-phase reaction between photochemically produced hydroxyl radicals and organic chemical.
Reliability	:	(2) valid with restrictions Estimation based on an EPA-accepted estimation model.
Flag	:	Critical study for SIDS endpoint

24.10.2002 (1)

3.1.2 STABILITY IN WATER

3.1.3 STABILITY IN SOIL

3.2 MONITORING DATA

3.3.1 TRANSPORT BETWEEN ENVIRONMENTAL COMPARTMENTS

Type	:	fugacity model level III
Media	:	other
Air (level I)	:	1.25
Water (level I)	:	13.4
Soil (level I)	:	83.9
Biota (level II / III)	:	
Soil (level II / III)	:	1.42
Method	:	other
Year	:	2002
Method	:	Estimation using measured data where available and EPIWIN -derived inputs where otherwise needed; based on Meylan et al 1993 methodology as adopted from Mackay et al 1996. Derived assuming emissions equivalent to 1000 kg/hr each for air, water and soil. Input data used: Henry's LC=1.91e-006 atm-m3/mole (Henrywin program), Vapor Press=5.16e-007 mm Hg (Mpbpwin program), Liquid VP=9.6e-005 mm Hg (super-cooled), Melting Pt=255 deg C (user entry), Log Kow=3.57 (user entry), Soil Koc=1.52e+003 (calc. by model).
Result	:	The second Soil data point refers to Sediment concentration estimations.
Reliability	:	(2) valid with restrictions Used accepted estimation model recommended by US EPA.
Flag	:	Critical study for SIDS endpoint

24.10.2002 (1)

3.3.2 DISTRIBUTION

3.4 MODE OF DEGRADATION IN ACTUAL USE

3.5 BIODEGRADATION

Type	:	aerobic
Inoculum	:	
Concentration	:	100mg/l related to Test substance related to
Contact time	:	4 month
Degradation	:	= .2 % after 24 hour(s)
Result	:	under test conditions no biodegradation observed
Deg. Product	:	
Method	:	other
Year	:	1973
GLP	:	no
Test substance	:	other TS
Method	:	A Semi-Continuous Activated Sludge (SCAS) biodegradation test procedure was employed, patterned after the standard method as found in JAOCS 42:986 (1965) and JAOCS 46:432 (1969). Due to the low solubility of Tetrathal in water, sodium tetrachlorophthalatewas used in this test. The agent was added at a rate of 100 mg per 24 hr cycle. Direct UV spectroscopic analysis was used to determine loss from the aqueous phase after sludge filtration at predetermined points of analysis between day 16 and 122.
Result	:	Mean disappearance rate between study days 16 and 122 was 0.2+/-2.0. Sodium Tetrachlorophthalate appeared to be essentially inert with respect to any toxic effects on the bacterial sludge. No inhibition of the sludge growth rate was noted during the cours e of the testing.
Test substance	:	Sodium tetrachlorophthalate was used since the anhydride form was considered too insoluble to use in this assay.
Reliability	:	(2) valid with restrictions The methods used in this test have subsequently been standardized and codified in national and international test guidelines, hence supporting its use. While conducted prior to GLP codification, the results of this study have been well documented.
Flag	:	Critical study for SIDS endpoint

02.11.2002 (11)

3.6 BOD5, COD OR BOD5/COD RATIO

3.7 BIOACCUMULATION

3.8 ADDITIONAL REMARKS

4.1 ACUTE/PROLONGED TOXICITY TO FISH

Type	:	other
Species	:	
Exposure period	:	
Unit	:	mg/l
Analytical monitoring	:	
LC50	:	c = 7.086
Method	:	other
Year	:	2002
GLP	:	no
Test substance	:	
Method	:	Predictive value obtained from ECOSAR for a 96-hr fish EC50 of a Neutral Organic, based on following properties specific to TCPA and inserted into the program (mol. wt.= 285.9, log Kow = 3.57, water solubility =0.98 mg/L).
Result	:	Predicted value is above the level of water solubility (<0.98 mg/L) for TCPA.
Reliability	:	(2) valid with restrictions Value was derived from use of ECOSAR a program within EPIWIN, a predictive program recommended by EPA.
Flag	:	Critical study for SIDS endpoint

02.11.2002 (1)

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Type	:	static
Species	:	Daphnia magna (Crustacea)
Exposure period	:	48 hour(s)
Unit	:	mg/l
Analytical monitoring	:	no
NOEC	:	= 180
EC50	:	> 1000
Method	:	other
Year	:	1984
GLP	:	yes
Test substance	:	other TS
Method	:	Study design followed recommendations from the US EPA Committtee on Methods for Toxicity Testing with Aquatic Organisms, 1975. Groups of 10 first instar D. magna were exposed to one of 5 test concentrations ranging in logarithmic series from 100 to 1000 mg/l (i.e. 100, 180, 320, 560 and 1000 mg/l). Each group was placed in a 250 ml glass beaker filled with 200 ml well water, held at 20 degrees C. with 16 hrs artificial light per day @ 50-70 footcandles. Test article was suspended in 1 ml acetone and added to the respective beaker. A solvent control and untreated control group were also run. All test concentrations were evaluated in duplicate. Daphnia were observed every 24 hrs for morbidity and mortality. Water quality indices (temp., pH, dissolved oxygen) were measured prior to study start and at the end of the study. Water hardness was between 225-275 ppm. LC50 values (24 and 48 hr) were calculated using the method of Stephen, Busch, Smith, Burke and Anderson, USEPA Duluth Labs computer model, 1978.
Result	:	White precipitate was observed at the top of all beakers containing test article. Insufficient deaths occurred at either 24 or 48 hrs to calculate an LC50. Thus, the LC50 is considered to be > 1000 mg/L at each time point.Water quality indices were diss. oxygen - 6.1-8.1 mg/L, temp. of 20 degrees C., and pH of 8.1-8.5; all were judged within acceptable limits. However, it is recognized that even the low dose used in this study exceeded the limit (<1 mg/l) of solubility of TCPA.

exceeded the limit (<1 mg/l) of solubility of TCPA.

Test substance	:	Purity of 99%
Reliability	:	(2) valid with restrictions EC50 value is excessive as this study was conducted at test levels above solubility; however, it can be stated that no toxic effects were observed at the limits of solubility in an otherwise well conducted study. ECOSAR predicted a 48-hr Daphnid LC50 (using EPIWIN, 2002) value for a Neutral Organic of 8.463 mg/L which is above the limit of solubility of TCPA [parameters entered were log Kow of 3.57, mol wt. of 285.9, and water solubility of 0.98 mg/L].
Flag	:	Critical study for SIDS endpoint

02.11.2002 (6)

4.3 TOXICITY TO AQUATIC PLANTS E.G. ALGAE

Species	:	Selenastrum sp. (Algae)
Endpoint	:	other
Exposure period	:	
Unit	:	mg/l
Analytical monitoring	:	
EC50	:	c = 5.791
Method	:	other
Year	:	2002
GLP	:	no
Test substance	:	
Method	:	Predictive value obtained from ECOSAR for a 96-hr green algae EC50 of a Neutral Organic, based on following properties specific to TCPA and inserted into the program (mol. wt.= 285.9, log Kow = 3.57, water solubility =0.98 mg/L).
Result	:	Predicted value is above the level of water solubility (<0.98 mg/L) for TCPA.
Reliability	:	(2) valid with restrictions Value was derived from use of ECOSAR a program within EPIWIN, a predictive program recommended by EPA.
Flag	:	Critical study for SIDS endpoint

02.11.2002 (1)

4.4 TOXICITY TO MICROORGANISMS E.G. BACTERIA

4.5.1 CHRONIC TOXICITY TO FISH

4.5.2 CHRONIC TOXICITY TO AQUATIC INVERTEBRATES

4.6.1 TOXICITY TO SOIL DWELLING ORGANISMS

4.6.2 TOXICITY TO TERRESTRIAL PLANTS

4.6.3 TOXICITY TO OTHER NON-MAMM. TERRESTRIAL SPECIES

4.7 BIOLOGICAL EFFECTS MONITORING

4.8 BIOTRANSFORMATION AND KINETICS

4.9 ADDITIONAL REMARKS

5.1.1 ACUTE ORAL TOXICITY

Type	:	LD0
Species	:	rat
Strain	:	Sprague-Dawley
Sex	:	male/female
Number of animals	:	12
Vehicle	:	other
Value	:	> 15800 mg/kg bw
Method	:	other
Year	:	1965
GLP	:	no
Test substance	:	other TS
Method	:	Administered as a 33% corn oil suspension via single dose gavage to groups of fasted rats at dosages of 500 (1 F), 1000 (1 M), 1580 (1F), 2510 (1M), 3980 (1F), 5010 (1M, 1F), 10000 (1M:1F) and 15800 (2M:1F) to define a Minimum Lethal Dose. Animals were observed for clinical signs daily and weighed on day 0 and day 5.
Result	:	No deaths occurred; some weakness and severe diarrhea were observed.
Test substance	:	99% purity
Conclusion	:	Acceptable study to define the low acute oral toxicity since dosage levels far exceeded current Limit Test standard used today. When test groups are combined, a total of 6M and 5F rats were dosed at test levels equal to or greater than the internationally accepted Limit Test value of 1,000 mg/kg; no deaths were recorded at any of these test levels such that it can be concluded that the LD50 (also the Minimum Lethal Dose or LD0) exceeds 1000 mg/kg.
Reliability	:	(2) valid with restrictions Conducted prior to GLP requirements, but adequately documented; also used limited no. animals per treatment group.
Flag	:	Critical study for SIDS endpoint

25.09.2002 (12)

5.1.2 ACUTE INHALATION TOXICITY

Type	:	LC0
Species	:	rat
Strain	:	Sprague-Dawley
Sex	:	male/female
Number of animals	:	20
Vehicle	:	no data
Exposure time	:	4 hour(s)
Value	:	> 3.6 mg/l
Method	:	other
Year	:	1975
GLP	:	no
Test substance	:	other TS
Method	:	Groups of 5 male and 5 female rats were exposed to atmospheres containing either 3.16 or 3.60 mg/l. test material for 4 hrs. Air concentrations were generated using a ferris wheel generator to create a dust and passing clean air through the generator at 30 L/min. to an 80 L. glass and steel chamber containing the animals. Particle size means were calculated. Rats were held for 14 days for observation, then sacrificed and necropsied. Physical signs were recorded.
Result	:	No deaths occurred at either test level. 3.6 mg/L was determined to be the maximum attainable concentration using this equipment. No untoward reactions were observed during the exposure or observation periods nor were there any alterations attributable to test material seen at necropsy.

were there any alterations attributable to test material seen at necropsy. Greater than 43 % of the dust particles were < 5 microns in diameter, and > 65% were less than 10 microns.

Test condition : Test material purity of 99%

Reliability : (2) valid with restrictions
Study was conducted prior to GLPs and test guidelines; had limited documentation, but is useful in arriving at lower limit of inhalation toxicity potential in that the maximum achievable atmospheric concentration did not produce lethality after acute exposure.

25.09.2002 (10)

5.1.3 ACUTE DERMAL TOXICITY

Type : LD0
Species : rabbit
Strain : New Zealand white
Sex : male/female
Number of animals : 6
Vehicle : other
Value : > 5010 mg/kg bw
Method : other
Year : 1965
GLP : no
Test substance : other TS
Method : Groups of single rabbits were treated dermally with either 501 (1F), 794 (1M), 1260 (1F), 2000 (1M), 3160 (1F) or 5010 (1M) mg/kg test article (ground powder in a 10% corn oil suspension) to define a Minimum Lethal Dose. All animals had their dorsal region closely shaved and test material applied to intact skin under an occlusive patch and held in place for 24 hours. Thereafter, the test article was wiped off. All animals were observed daily for signs of toxicity and weighed prior to and at study term (5 days).
Result : No deaths occurred in the study at any dose level; The only manifestation of toxicity was generalized reduced activity.
Test substance : Purity of 99%
Conclusion : Data is sufficient to establish low acute toxicity by dermal route as most of the dose levels exceeded the Limit Test dosage.
Reliability : (2) valid with restrictions
Conducted before GLP requirements but is adequately documented. Limited no. of animals and shorter duration for observation used.

27.08.2002 (12)

5.1.4 ACUTE TOXICITY, OTHER ROUTES

5.2.1 SKIN IRRITATION

5.2.2 EYE IRRITATION

5.3 SENSITIZATION

5.4 REPEATED DOSE TOXICITY

Species : rat

Sex	:	male/female
Strain	:	Fischer 344
Route of admin.	:	gavage
Exposure period	:	Five days per week for 13 weeks
Frequency of treatment	:	Once daily
Post obs. period	:	none
Doses	:	0, 94, 187, 375, 750 or 1500 m/kg/d
Control group	:	yes, concurrent vehicle
NOAEL	:	< 94 mg/kg bw
LOAEL	:	= 94 mg/kg bw
Method	:	OECD Guide-line 408 "Subchronic Oral Toxicity - Rodent: 90-day Study"
Year	:	1987
GLP	:	yes
Test substance	:	other TS
Method	:	This study was conducted under the auspices of the US National Toxicology Program (NTP). Ten (10) male and 10 female F344 rats of approx 6 weeks of age were administered TCPA in corn oil by gavage at doses of 0, 94, 187, 375, 750 or 1500 mg/kg/d for 5 days/week, for 13 consecutive weeks. Animals were housed, 5/cage, in stainless steel mesh cages with water and diet available ad libitum. Animal rooms were maintained at 67-77 degrees F and between 30-70% rel. humid, and had at least 10 room air changes/hr and a 12 hr light:dark cycle. All animals were observed twice daily for morbidity and mortality and detailed clinical signs were recorded on a weekly basis. Food consumption was recorded weekly by cage and individual body weights were recorded at study initiation and then weekly thereafter until study term. All rats underwent a hematology evaluation (RBC, HCT, HGB, MCH, MCHC, MCV, WBC, differential/morphological leukocyte exams, reticulocyte analysis and platelet counts) at the end of the study. Clinical chemistries (ALT, ALB, CRET, GGT, GLU, BUN) were analyzed on study days 6, 20, and at study term for all rats on test. Absolute and relative weights were recorded for the following organs of all rats at study term: brain, heart, kidney, liver, lung, spleen, testis (males only), and thymus. Complete necropsies were performed on all animals. Over 40 organs and tissues were examined for gross lesions and fixed in 10% neutral buffered formalin. Complete histopathologic examinations were performed on all control animals, on all animals in the highest dose group with at least 60% survivors, and on all animals, including those that died or were killed moribund before the end of the study, in the higher dose groups. The kidneys were identified as a target organ, hence kidneys were evaluated for all males and females at all dose levels, along with any gross lesions observed in-life. Organ and body weight data, which are approximately normally distributed, were analyzed statistically using parametric multiple comparison procedures outlined by Williams (1971/1972 Biometrics 27: 103 & 519) or Dunnett (1955. J. Am. Stat. Assoc. 50:1096). Hematology and clinical chemistry data, which typically have skewed distributions, were analyzed using the nonparametric multiple comparisons methods of Shirley (1977. Biometrics 33:386.) or Dunn (1964. Technometrics 6:241). Jonckheere's test (1954. Biometrika 41:133) was used to assess the significance of dose-response trends and to determine whether a trend-sensitive test was more appropriate for pairwise comparisons than a test capable of detecting departures from monotonic dose response. P-values were set at < 0.01. No ophthalmoscopic exam, consistent with Guideline 408, was conducted.
Remark	:	No effects on organ weight or morphology was observed for any of the gonads (male and female) in this study.
Result	:	Treatment-related deaths occurred at 1500 mg/kg (5/10 males; 1/10 females) and 750 mg/kg (1/10 females). Mean final body weights and weight gains were statistically significantly reduced in groups of male rats given 375, 750 and 1500 mg/kg TCPA and in all female TCPA-treated groups. All groups (males and females) at all treatment levels exhibited decreased feed consumption compared to controls. No compound-specific clinical signs of toxicity were observed at any test level. Absolute and

clinical signs of toxicity were observed at any test level. Absolute and relative kidney weights were increased in a dose-dependent manner to female rats while males were significantly increased (relative wt) at 187 mg/kg and higher. Other changes (spleen, thymus and liver)were either small, inconsistent or attributed to the marked decrease in body weights exhibited, and thus were not considered treatment-related. Changes in several hematology and clinical chemistry parameters were judged as minor and sporadic and were not considered clinically significant. No gross lesions attributable to treatment were observed at necrospy. Treatment-related microscopic lesions were identified in the kidney of male and female rats from all test groups, and consisted of renal tubular degenerative changes. These changes involved epithelial necrosis at higher dose levels and tubular dilation at lower dose levels. No other microscopic findings attributable to treatment were found.Thus, a NOEL was not established in this study.

Test substance : Test substance was 99% pure.
Reliability : (2) valid with restrictions
Used a reduced no. of clinical chemistry parameters and no in-life ophthalmoscopic exam.
Flag : Critical study for SIDS endpoint
02.11.2002 (5)

Species : mouse
Sex : male/female
Strain : B6C3F1
Route of admin. : gavage
Exposure period : 5 Days/week for 13 weeks
Frequency of treatment : Once per day
Post obs. period : none
Doses : 0, 94, 187, 375, 750, or 1500 mg/kg/d
Control group : yes, concurrent vehicle
NOAEL : >= 187 mg/kg bw
LOAEL : = 375 mg/kg bw
Method : other
Year : 1992
GLP : yes
Test substance : other TS
Method : This study was conducted under the auspices of the US National Toxicology Program (NTP). Ten (10) male and 10 female B6C3F1 mice of approx 5 weeks of age were administered TCPA in corn oil by gavage at doses of 0, 94, 187, 375, 750 or 1500 mg/kg/d for 5 days/week, for 13 consecutive weeks. Animals were individually housed in stainless steel mesh cages with water and diet available ad libitum. Animal rooms were maintained at 67-77 degrees F and between 30-70% rel. humid, and had at least 10 room air changes/hr and a 12 hr light:dark cycle. All animals were observed twice daily for morbidity and mortality and detailed clinical signs were recorded on a weekly basis. Food consumption was recorded weekly for each animal and individual body weights were recorded at study initiation and then weekly thereafter until study term. All mice underwent a hematology evaluation (RBC, HCT, HGB, MCH, MCHC, MCV, WBC, differential/morphological leukocyte exams, reticulocyte analysis and platelet counts) at the end of the study. No clinical chemistries or ophthalmoscopic exams were performed. Absolute and relative weights were recorded for the following organs of all mice at study term: brain, heart, kidney, liver, lung, spleen, testis (males only), and thymus. Complete necropsies were performed on all animals. Over 40 organs and tissues were examined for gross lesions and fixed in 10% neutral buffered formalin. Complete histopathologic examinations were performed on all control animals, on all animals in the highest dose group with at least 60% survivors, and on all animals, including those that died or were killed moribund before the end of the study, in the higher dose groups. Organ and body weight data, which are approximately normally distributed, were

and body weight data, which are approximately normally distributed, were analyzed statistically using parametric multiple comparison procedures outlined by Williams (1971/1972 Biometrics 27: 103 & 519) or Dunnett (1955. J. Am. Stat. Assoc. 50:1096). Hematology data, which typically has a skewed distribution, were analyzed using the nonparametric multiple comparisons methods of Shirley (1977. Biometrics 33:386.) or Dunn (1964. Technometrics 6:241). Jonckheere's test (1954. Biometrika 41:133) was used to assess the significance of dose-response trends and to determine whether a trend-sensitive test was more appropriate for pairwise comparisons than a test capable of detecting departures from monotonic dose response. P-values were set at < 0.01.

Result : One female mouse died at 750 mg/kg; all other animals survived the test period, and thus this death was not attributed to treatment. No differences were observed in feed consumption or final body weights that were attributed to TCPA. No clinical signs of toxicity were observed. No clearly discernable effect of treatment could be made on organ weight changes. A dose-related decrease in HGB concentration was observed in male mice given 375 mg/kg and higher TCPA and in females given 750 mg/kg or above. Decreases in HCT and RBC also were observed in male mice given 1500 mg/kg. No treatment-related gross lesions were seen at necropsy nor where any treatment-related microscopic lesions identified after microscopic examination of tissues. No effects on the testes were observed.

Test substance : Reported as 99% pure

Reliability : (2) valid with restrictions
No clinical chemistry or in-life ophthalmoscopic exams were conducted.

02.11.2002 (5)

Species : rat
Sex : male/female
Strain : Sprague-Dawley
Route of admin. : inhalation
Exposure period : 6 hr/d, 5d/week for 13 weeks
Frequency of treatment : daily, 5d/week
Post obs. period : none
Doses : 0, 0.5, 5 and 50 mg/m3 (nominal) and 0, 0.73, 4.15 and 36.3 mg/m3 (analytical), respectively
Control group : yes, concurrent vehicle
NOAEL : < .73 mg/m³
Method : other
Year : 1982
GLP : no
Test substance : other TS
Method : Groups of 15 male and 15 female rats exposed to atmospheric dust levels targeted at 0, 0.5, 5 and 50 mg/m3 for 6 hr/d, 5d/week for 13 weeks. Animals exposed in stainless steel and glass cages; whole body exposures. Air flow rate of approximately 280 L/min, during which test agent was added using a Wright dust feed device. Chamber concentrations were analyzed using a GCA Respirable dust monitor for the first 5 weeks and then spectrophotometrically during the remainder of the study. Analytical exposure levels for the first 5 weeks were calculated by extrapolation based on regression analysis of daily nominal concentrations. Daily analytical concentrations were used for the last 8 weeks of the study. Correlation coefficients for regression analysis of analytical and nominal concentrations was 0.97 for the low, mid and high doses combined,and was 0.90 for the high and mid dose, but only 0.50 for the low dose; hence the low dose level may not be accurately described. Particle size distribution was determined using a Batelle cascade impactor. Animals were observed twice daily for morbidity and mortality and weekly for detailed physical examinations and body weight. At 7 and 13 week intervals, the following clinical parameters were measured for all surviving control and high dose animals: hematology (HGB, HCT, RBC, Clotting

control and high dose animals: hematology (HGB, HCT, RBC, Clotting time, total and differential leukocytes), blood chemistries (ALP, BUN, SGPT, GLU), and urinalysis (gross appearance, spec. grav. pH, PRO, GLU, ketones, Bilirubin, occult blood and microscopic elements). Complete necropsies were conducted on all surviving animals after 13 weeks and organ weights and weight ratios (body and brain) were recorded for: brain, ovaries, testes, kidneys, heart, liver, lungs, pituitary and spleen. Microscopic examination of the following tissues were performed for all control and high dose rats: adrenals, bone marrow, brain, eyes, heart, colon, duodenum, ileum, kidneys, liver, lungs, lymph nodes, mammary gland, ovaries, pancreas, pituitary, prostate, salivary gland, skeletal muscle, skin, spinal cord, spleen, stomach, testes with epididymus, thyroid, parathyroid, unrinary bladder and uterus. Lungs were also evaluated for all surviving animals in the mid and low dose groups. Mean group values for body weights, organ weights and weight ratios were evaluated statistically using Dunnett's test (J AM Stat Assn. 1955. vol 50:1096 and Biometrics 20:482, 1964). The F-test and Students' T test were used to compare group means for hematology and clinical chemistry parameters. When variances were observed in the F-test, a Student's t test, as modified using Cochran's approximation test was employed (Snedecor, GS. Statistical Methods. 1967. Iowa State University Press.) All comparisons were made at both the 5% and 10% level of significance.

Result : Cumulative mean analytical concentrations were 0.73, 4.15, and 36.3 mg/m3 respectively based on spectrophotometric analysis of chamber samples. Although the mean analytical chamber concentrations for the low and mid level appear close to target levels, extreme variations in chamber concentrations were observed from day to day and also during any given day. At the high dose level, similar daily excursions occurred. In general, during weeks 2 through 5, animals appeared to have been exposed to concentrations well below the target levels; the mean nominal concentration for the low, mid and high-dose level were 9, 17.7 and 198 mg/m3. The mean aerodynamic mass median diameter fo the low, mid and high levels were 2.69, 3.34 and 3.45 micrometers, respectively. All animals survived the study duration. Physical observations were limited to the high dose group, and consisted of increased nasal discharge, ano-genital staining and excessive lacrimation.Body weight gains for all levels for both sexes were considered comparable to controls. Clinical blood parameters were considered unaffected by treatment. High dose males exhibited slight proteinuria at 7 weeks and 13 weeks. Microscopic examination of the urine revealed a slight increase in the amount of amorphous matter in the urine after 13 weeks. An increase in absolute and relative lung weights in the mid-dose males and high dose males and females were considered treatment-related. The several other small changes in organ weights or ratios were considered unrelated to treatment since there was no dose-response evident.The only gross pathological observation attributable to treatment was the appearance of petechial hemorrhages in the lungs of several treated rats. Histopathological changes in the lungs were also noted in all dose groups. Irregular thickening of the alveolar septa, scattered pigmented macrophages and multinucleate giant cells, multifocal accumulation of alveolar macrophages and multifocal alveolar hemorrhages were noted. High dose animals also exhibited mild centrilobular hepatocellular hypertrophy. No effects, either in organ weight or pathology (gross and histo-) were noted for either the ovaries or testes/epididymides of rats treated at any dose level.

Test substance : Dust of product-specific Fines; test material was 99% pure.

Reliability : (2) valid with restrictions
In view of the excursions in exposure concentrations and the problems of extrapolation of analytical concentrations at the low dose level, the accuracy of this dose level is questionable.

27.08.2002 (7)

Species : rat

Sex	:	male/female
Strain	:	Sprague-Dawley
Route of admin.	:	inhalation
Exposure period	:	6 hours/day, 5 days/week for 13 weeks
Frequency of treatment	:	5 days/week for 13 weeks
Post obs. period	:	none
Doses	:	0, 0.5, 5 and 50 mg/m3 (nominal targets)
Control group	:	yes, concurrent no treatment
NOAEL	:	< .5 mg/m³
Method	:	other
Year	:	1982
GLP	:	no
Test substance	:	other TS
Method	:	Groups of 15 male and 15 female rats were exposed to atmospheric fume levels targeted at 0, 0.5, 5 and 50 mg/m3 for 6 hr/d, 5d/week for 13 weeks. Fumes were created by passing a stream of air through a flask containing the test material and heated to 200 degrees C. Animals were exposed via whole body in 1 M3 stainless steel and glass chambers. Air flow rates were approximately 280 L/min. Chamber concentrations were analyzed using a GCA Respirable dust monitor for the first 5 weeks and then spectrophotometrically during the remainder of the study. Analytical exposure levels for the first 5 weeks were calculated by extrapolation based on regression analysis of daily nominal concentrations. Daily analytical concentrations were used for the last 8 weeks of the study. Correlation coefficients for regression analysis of analytical and nominal concentrations were 0.87 for the low, mid and high doses combined, 0.69 for the high and mid dose, but only 0.12 for the low dose; hence the low dose level may not be accurately described. Particle size distribution was determined using a Batelle cascade impactor. Animals were observed twice daily for morbidity and mortality and weekly for detailed physical examinations and body weight. At 7 and 13 week intervals, the following clinical parameters were measured for all surviving control and high dose animals: hematology (HGB, HCT, RBC, Clotting time, total and differential leukocytes), blood chemistries (ALP, BUN, SGPT, GLU), and urinalysis (gross appearance, spec. grav. pH, PRO, GLU, ketones, Bilirubin, occult blood and microscopic elements). Complete necropsies were conducted on all surviving animals after 13 weeks and organ weights and weight ratios (body and brain) were recorded/calculated for: brain, ovaries, testes, kidneys, heart, liver, lungs, pituitary and spleen. Microscopic examination of the following tissues were performed for all control and high dose rats: adrenals, bone marrow, brain, eyes, heart, colon, duodenum, ileum, kidneys, liver, lungs, lymph nodes, mammary gland, ovaries, pancreas, pituitary, prostate, salivary gland, skeletal muscle, skin, spinal cord, spleen, stomach, testes with epididymus, thyroid, parathyroid, unrinary bladder and uterus. Lungs were also evaluated for all surviving animals in the mid and low dose groups. Mean group values for body weights, organ weights and weight ratios were evaluated statistically using Dunnett's test (J AM Stat Assn. 1955. vol 50:1096 and Biometrics 20:482, 1964). The F-test and Students' T test were used to compare group means for hematology and clinical chemistry parameters. When variances were observed in the F-test, a Student's t test, as modified using Cochran's approximation test was employed (Snedecor, GS. Statistical Methods. 1967. Iowa State University Press.) All comparisons were made at both the 5% and 10% level of significance.
Result	:	Cumulative mean analytical exposure concentrations were 0.5, 5.6 and 26.6 mg/m3 respectively, for the low, mid and high dose levels, based on spectrophotometric analysis and regression analysis. Although the mean analytical chamber concentrations for the low and mid-dose level appear to be close to target levels, extreme variations in chamber concentrations were observed from day to day and also during any given day at all dose levels. The respective mean nominal concentrations for the low, mid and high dose levels were 1.6, 13 and 57 mg/m3, respectively. The mean

high dose levels were 1.6, 13 and 57 mg/m3, respectively. The mean aerodynamic mass median diameter for these levels were: 2.6, 2.5 and 1.7 micrometers. All animals survived the study duration. Physical observations were limited to the high dose group, and consisted of increased red nasal discharge and dry rales. Body weight gains for all treated levels for both sexes were considered comparable to controls. Clinical blood parameters were considered unaffected by treatment at both time points, with the exception of a increase in blood glucose levels seen in both males and females (statistically significantly increased) after 13 weeks of testing. No treatment-related effects were observed after urinalysis at either study interval. Lung weights in high dose males and females were significantly increased over control group levels and appeared dose-related. The several other small changes in organ weights or ratios were considered unrelated to treatment since there was no dose-response evident. The only gross pathological observation attributable to treatment was the appearance of petechial hemorrhages in the lungs of several treated rats. Histopathological changes in the lungs were also noted in all dose groups. Irregular thickening of the alveolar septa, scattered pigmented macrophages and multinucleate giant cells, multifocal accumulation of alveolar macrophages and multifocal alveolar hemorrhages were noted. High dose animals also exhibited mild centrilobular hepatocellular hypertrophy. No effects, either in organ weight or pathology (gross and histo-) were noted for either the ovaries or testes/epididymides of high dose-treated rats.

Test substance : Dust of product-specific Fines fumes; test material was 99% pure.

Reliability : (2) valid with restrictions
In view of the excursions in exposure concentration and the problems of extrapolation of analytical concentrations at the low dose level, the accuracy of this dose level is questionable.

05.09.2002 (8)

5.5 GENETIC TOXICITY 'IN VITRO'

Type : Ames test
System of testing : S. tymphimurium TA-1535, TA-1537, TA98 and TA100
Concentration : Test # 1-0, 33.3, 100, 333.3, 1000, 3333.3 and 6666.7 ug/plate; Test # 2-0, 1, 3.3, 10, 33, 100, 333, 1000 ug/plate
Cycotoxic conc. : Test # 1 - 3333.3 ug/plate; Test # 2 - > 1000 ug/plate
Metabolic activation : with and without
Result : negative
Method : OECD Guide-line 471 "Genetic Toxicology: Salmonella thyphimurium Reverse Mutation Assay"
Year : 1985
GLP : yes
Test substance : other TS
Method : Two independently conducted studies were performed, each conducted at a separate contract facility for the US NTP. Test design met OECD Guideline 471. TCPA was incubated with S. typhimurium tester strains either in buffer or S9 mix (from Arochlor 1254-treated male SD rats or Syrian hamsters) for 20 min. at 37 degrees C. Top agar supplemented with l-histidine and d-biotin was added and the contents of the tubes were mixed and poured onto the surfaces of minimal glucose agar plates. Histidine-independent mutant colonies arising on these plates were counted following incubation for 2 days at 37 degrees C. Each trial consisted of triplicate plates of concurrent positive and negative controls and of at least 5 doses of TCPA. All assays were repeated in duplicate.
Result : TCPA was negative in four tester strains, in both trials, at both laboratories, with and without metabolic activiation using hamster and rat S9 mix.
Test substance : Test substance reportedly 99% pure.
Reliability : (1) valid without restriction

Flag	:	Critical study for SIDS endpoint
25.09.2002		(14)
Type	:	Cytogenetic assay
System of testing	:	Chinese Hamster Ovary Cell in vitro Assay (SCEs and Chrom. Abbs).
Concentration	:	0, 25, 75, 125, 250, 500 and 750 ug/mL.
Cycotoxic conc.	:	> 750 ug/mL.
Metabolic activation	:	with and without
Result	:	negative
Method	:	other
Year	:	1987
GLP	:	yes
Test substance	:	other TS
Method	:	Studies conducted according to NTP study design such that both SCEs and Chrom. Abb. were identified both in the presence and absence of SD male rat Arochlor 1254-induced liver S9 fractions. Cell cultures were handled to prevent photolysis of Brdu-substituted DNA. Each test consisted of concurrent solvent and positive controls and at least 3 doses of TCPA. A single flask per dose was used and trials yielding equivocal or positive results were repeated. In the SCE test, cells were incubated for 26 hrs with TCPA in McCoy's 5A medium supplemented with fetal bovine serum, l-glutamine and antibiotics. BrdU was added 2 hrs after culture initiation; 26 hrs later the medium containing TCPA was removed and replaced with fresh medium plus BrdU and colcemid and incubated another 2 hrs. Cells were harvested by mitotic shake-off, fixed and stained with Hoechst 33258 and Giemsa. In the SCE test with S9, cells were incubated with test material, serum-free medium and S9 for 2 hrs. All slides were scored blind, with 50 second-division metaphase cells scored for frequency of SCEs/cell from each dose level. In the Chrom Abs test, cells were incubated in McCoy's 5A medium with test agent for 12 hrs (cells were treated with TCPA and S9 for 2 hrs), colcemid added and incubated for an additional 2 hrs and harvested in a fashion similar to the SCE study portion. 100 first-division metaphase cells were scored blind from prepared slides for each dose level. Classes of aberrations were recorded and included simple, complex and other abnormalities. Statistical analyses (Armitage trend test) were conducted on the slopes of the dose-response curves, with a SCE frequency 20% above the concurrent solvent control value chosen as a conservative positive response; $p<0.01$. For evaluation of chrom osomal aberrations, statistical analyses (Armitage trend test; Margolin multiple comparison) were conducted on both the dose-response curve and individual dose points, significance was determined as $p<0.05$ for single data points and $p<0.015$ for trend.
Result	:	TCPA did not induce SCEs or chromosomal aberrations in Chinese hamster ovary cells with or without metabolic activation. In the SCE study, a positive response was seen with S9, but was not confirmed in a subsequent trial and thus was judged as unrelated to TCPA treatment.
Test substance	:	Test substance was 99% pure.
Reliability	:	(2) valid with restrictions Combined Chromosomal Aberration and SCE study following NTP study design. Was well documented and useful for regulatory purposes.
Flag	:	Critical study for SIDS endpoint
25.09.2002		(2)

5.6 GENETIC TOXICITY 'IN VITRO'

5.7 CARCINOGENITY

5.8 TOXICITY TO REPRODUCTION

Type	:	other
Species	:	rat
Sex	:	male/female
Strain	:	Fischer 344
Route of admin.	:	gavage
Exposure period	:	5 days per week for 13 weeks
Frequency of treatment	:	once per day
Premating exposure period		
Male	:	
Female	:	
Duration of test	:	13 weeks
Doses	:	0, 94, 357, 750 and 1500 mg/kg
Control group	:	yes, concurrent vehicle
NOAEL Parental	:	>= 1500 mg/kg bw
Method	:	other
Year	:	1987
GLP	:	yes
Test substance	:	other TS
Method	:	Evalutions performed in conjuction with a 13 week NTP study referenced in Repeated Dose Robust Summary section. Sperm morphology was performed on male rats exposed to 0, 94, 375 and 750 mg/kg TCPA at the conclusion of the 13 week study. At necropsy, the right epididymis was isolated and weighed. The tail of the epididymis was then removed from the epididymal body and weighed. Test yolk or Tyrode's buffer was applied to slides and a small incision was made at the distal border of the epididymal tail. The sperm effluxing from the incision were dispersed in the buffer on the slides and the numbers of motile and nonmotile spermatozoa were counted for 5 fields per slide. Sperm density was then determined microscopically with the aid of a hemacytometer after the caudal tissue was incubated in saline and then heat fixed. Statistical treatment was performed using either Dunn's test or Shirley's test or Dunnett's test, as described in the Repeat Dose section of this dossier. Vaginal cytology evaluations were performed on female rats from the 0, 94, 375 and 1500 mg/kg dose groups. Seven days prior to sacrifice, the vaginal vaults of the females of each species and dose group were lavaged and the aspirated fluid and cells stained with Toluidine Blue. Relative numbers of leukocytes, nucleated epithelial cells, and large squamous epithelial cells were determined and were used to ascertain estrous cycle stage. An arcsine transformation was used to bring the proportion data into closer conformance with normality assumptions before additional statistical treatment was performed. Effects of treatment were investigated by applying a multivariate analysis (MANOVA) of variance to the transformed data to test for the simultaneous equality of measurement across dose levels.
Remark	:	Sperm Morphology and Vaginal Cytology Evaluation
Result	:	No changes between exposed animals and controls in sperm morphology and vaginal cytology were considered of biological significance for any of the parameters evaluated.
Test substance	:	Test material reported as 99% pure
Reliability	:	(4) not assignable Study design does not meet that needed to fulfill this Endpoint; results appear reliable but not conducted according to a standardized protocol.

27.08.2002 (5)

Type	:	other
Species	:	mouse
Sex	:	male/female
Strain	:	B6C3F1

Route of admin.	:	gavage
Exposure period	:	5 days per week for 13 weeks
Frequency of treatment	:	once per day
Premating exposure period		
Male	:	
Female	:	
Duration of test	:	13 weeks
Doses	:	0, 94, 375 and 1500 mg/kg
Control group	:	yes, concurrent vehicle
NOAEL Parental	:	>= 1500 mg/kg bw
Method	:	other
Year	:	1987
GLP	:	yes
Test substance	:	other TS
Method	:	Evalutions performed in conjuction with a 13 week NTP study referenced in Repeated Dose Robust Summary section. Sperm morphology was performed on male mice exposed to 0, 94, 375 and 1500 mg/kg TCPA at the conclusion of the 13 week study. At necropsy, the right epididymis was isolated and weighed. The tail of the epididymis was then removed from the epididymal body and weighed. Tyrode's buffer was applied to slides and a small incision was made at the distal border of the epididymal tail. The sperm effluxing from the incision were dispersed in the buffer on the slides and the numbers of motile and nonmotile spermatozoa were counted for 5 fields per slide. Sperm density was then determined microscopically with the aid of a hemacytometer after the caudal tissue was incubated in saline and then heat fixed. Statistical treatment was performed using either Dunn's test or Shirley's test or Dunnett's test, as described in the Repeat Dose section of this dossier. Vaginal cytology evaluations were performed on female mice from the 0, 94, 375 and 1500 mg/kg dose groups. Seven days prior to sacrifice, the vaginal vaults of the females of each dose group were lavaged and the aspirated fluid and cells stained with Toluidine Blue. Relative numbers of leukocytes, nucleated epithelial cells, and large squamous epithelial cells were determined and were used to ascertain estrous cycle stage. An arcsine transformation was used to bring the proportion data into closer conformance with normality assumptions before additional statis tical treatment was performed. Effects of treatment were investigated by applying a multivariate analysis (MANOVA) of variance to the transformed data to test for the simultaneous equality of measurement across dose levels.
Remark	:	Sperm Morphology and Vaginal Cytology Evaluation
Result	:	Sperm morphology evaluations revealed a statistically significant decrease to sperm motility in male mice at 1500 mg/kg; however, values were not decreased relative to historical control data. Thus, it was concluded that TCPA did not affect any of the parameters measured in this study.
Test substance	:	Test material reported purity of 99%.
Reliability	:	(4) not assignable Study design does not meet that needed to fulfill this Endpoint; results appear reliable but not conducted according to a standardized protocol.

27.08.2002 (5)

5.9 DEVELOPMENTAL TOXICITY/TERATOGENICITY

Species	:	rat
Sex	:	female
Strain	:	Sprague-Dawley
Route of admin.	:	gavage
Exposure period	:	Dosing on gestation days 6 through 19

Frequency of treatment	:	Daily dose administered during gestation days 6-19
Duration of test	:	Animals sacrificed on gestation day 20
Doses	:	0, 250, 1000 and 2000 mg/kg/d
Control group	:	yes, concurrent vehicle
NOAEL Maternalt.	:	= 1000 mg/kg bw
NOAEL Teratogen	:	= 1000 - mg/kg bw
Method	:	OECD Guide-line 414 "Teratogenicity"
Year	:	1982
GLP	:	yes
Test substance	:	other TS
Method	:	Groups of 24 mated female rats were dosed daily by gavage (test material dissolved/suspended in corn oil) during gestation days 6 -19 at dosage levels of 0, 250, 1000 and 2000 mg/kg/d. Stability and homogeneity of the dosing solution were determined prior to initiation of the study and accuracy of dose solutions analyzed throughout the study. All rats were observed for mortality and abnormal behavior twice daily from gestation day 0 through day 20, at which time all animals were sacrificed. Detailed physical exams for signs of toxicity were recorded on study days 0, 6, 10, 15 and 20. Maternal body weights were recorded at several intervals throughout the study. At sacrifice the uterine horns were examined for implantation sites, resorptions and the number of viable or non-viable fetuses. The number of corpora lutea were also recorded. The sex and weights of all live fetuses were recorded and all fetuses were examined for external abnormalities. One-half of the fetuses per litter were examined for skeletal malformations while the other half were examined for internal anomalies. The following statistical analyses were performed: For interval data (body wts, wt changes, reproductive data) -Bartlett's test was used to determine equality of variance and ANOVA and Dunnett's test used for parametric data while the Kruskal-Wallis test and Summed Rank test (Dunn) was used for nonparametric data (Snedecor and Cochran.; Hollander and Wolfe). For Incidence data i.e. mortality rates, % and incidence of variations and malformations - comparisons were made using the Chi-square contingency table and the 2X2 Fisher Exact test using the Bonferroni inequality estimate; linear trend was evaluated using the Armitage test. Comparisons were made using the litter as the comparative entity. Both the 5% and 10% level of statistical significance were reported for each parameter.
Result	:	Dosing solutions were shown to be homogeneous and stable and within 95% of the target concentrations. One female in each of the low and mid dosage groups and two females in the high dosage group died during the study, but were considered dosing error and not toxicity-related. Physical observations recorded included a lethargic appearance in several mid and high-dosage animals and pale eye color on day 20 of gestation in 4 rats in the 2000 mg/kg/d test group. Mean body weight gains in animals treated with the test article were comparable to controls. No treatment-related gross pathologic findings were seen at autopsy. Fetal body weights for male and female pups at 2000 mg/kg/d were significantly depressed when compared to controls; mid and low dose group mean pup weights were similar to controls. Pregnancy rates, mean nos. of corpora lutea, implantations, resorptions, live fetuses and fetal sex distribution were similar to control values. The incidence of external and soft tissue anomalies among treated groups was similar to controls both on a per litter and per fetus basis. The types and incidences of ossification variations were comparable between the 250 and 1000 mg/kg/d treated and control groups. At 2000 mg/kg/d, a slight increase in the incidence of asymetric/unossified sternebra and incompletely ossified thoracic vertebral centra were observed and are considered representative of a fetotoxic effect. The incidence of skeletal malformations was comparable between the control, low and mid dosage groups. At 2000 mg/kg/d, an increase in the incidence of rib and vertebral malformations was observed. The incidence of skeletal malformations, both on a per fetus and per litter basis was comparable between the control, low and mid dosage groups. At 2000

was comparable between the control, low and mid dosage groups. At 2000 mg/kg/d, the incidence of rib and vertebral malformations was slightly higher than concurrent controls and also higher than historical controls at the testing laboratory. While not statistically elevated, due to the unusual type of malformation seen and the relative lack of maternal toxicity at this level, this was considered to represent a teratogenic response. No maternal toxicity, embryotoxicity, fetotoxicity or teratogenic effects were observed at or below 1000 mg/kg/d.

Test substance : Purity of 99%.
Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
25.09.2002 (9)

5.10 OTHER RELEVANT INFORMATION

5.11 EXPERIENCE WITH HUMAN EXPOSURE

(1) EPIWIN. 2002. Version 3.10. 2002. Syracuse Research Corp., Syracuse, NY,

(2) Galloway et al, 1987. Environ. Mol. Mutagen.10: 1-175; also published in NTP Toxicity Report Series No. 28 (PB94119245), 1993.

(3) Hawley, GG. 1975. The Condensed Chemical Dictionary. 9th Ed. NY: Van Nostrand Reinhold Co. P. 845.

(4) NTP Chemical Repository, Catalog ID No. 000055.

(5) NTP Technical Report Series No 28, 1993 (NTIS PB94119245).

(6) Solutia study no. AB-90-9501. Acute toxicity of Tetrathal to Daphnia magna.

(7) Solutia study no. BD-78-189. A 13-week inhalation toxicity study of Tetrachlorophthalic anhydride fines-dust form in the rat.[EPA Document no. 88-920007306]

(8) Solutia study no. BD-78-190. A 13-week inhalation toxicity study of Tetrachlorophthalic anhydride fines-fume form in the rat. [EPA Document no. 88-920007094].

(9) Solutia study no. BD-81-268. A teratogenicity study in rats with CP 626 (Tetrachlorophthalic anhydride). [EPA Document No. 88-900000121; Fiche no. OTS0524050].

(10) Solutia study no. BT-74-91. Acute dust inhalation toxicity study with TETRATHAL.

(11) Solutia study no. MO20020123. Biodegradation testing of TETRATHAL.

(12) Solutia Study No. Y-65-50. Toxicological investigation of CP 626-2 (Tetrachlorophthalic anhydride).

(13) Weast, RC (ed) . 1979. Handbook of Chemistry and Physics. 60th Ed. Boca Raton, Fla,: CRC Press, Inc. p. C-438.

(14) Zeiger et al, 1985 Environ Muta gen 7:213-232; also in NTP Technical Report Series No. 28 (PB94119245), 1993.

7.1 END POINT SUMMARY

7.2 HAZARD SUMMARY

7.3 RISK ASSESSMENT